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# Inference of stochastic nonlinear equations for characterisation and prediction of prandial blood glucose levels

Yan Zhang\*, Natasha Khovanova\*, and Tim A. Holt \*\*

\**School of Engineering, University of Warwick, UK*

\*\**Department of Primary Care Health Sciences, Oxford University, UK*

**Summary.** Stochastic linear and nonlinear models describing response of blood glucose concentration to food intake for people with and without diabetes have been developed. A variational Bayesian approach has been applied in order to infer parameters of the models, and the best model was selected. The nonlinear models allow estimation of deterministic parameters and intensities of stochastic components, and can potentially be used for long term prediction of the glucose concentration response to external stimuli.

## Introduction

For more than half a century researchers have been working towards establishing an effective dynamic model describing and predicting glucose concentration level in humans. Glucose concentration is tightly regulated by a complex neuro-hormonal control system and can be influenced by various factors. Exogenous factors such as food intake, exercise, rate of digestion etc., deviate the glucose level from the basal level, while endogenous factors, including epinephrine, cortisol, growth hormone [1], and pancreatic endocrine hormones (insulin and glucagon) [2], serve as internal regulators to drive the glucose concentration level back to normal and maintain it. Insulin is the main regulator of glucose homeostasis. The glucose-insulin interaction comprises a feedback control system: when the blood glucose level rises, insulin is released from pancreatic  $\beta$ -cells to inhibit hepatic glucose production and promote glucose utilization so as to bring the glucose rapidly to the pre-perturbation level. If the glucose-insulin system is impaired, high levels of blood glucose (hyperglycaemia) or low levels (hypoglycaemia) may occur. The most common cause for hyperglycaemia is diabetes mellitus. In diabetes, hyperglycaemia is usually caused by low insulin levels (type I diabetes) and/or by resistance to insulin at the cellular level (type II diabetes). According to Cohen et al. [3], measures of 2-h glucose concentrations alone or combined with fasting concentration, body composition etc. are poor predictors of postprandial glycaemic exposure. Modern continuous glucose monitoring (CGM) has the advantage of obtaining hundreds of data points over a week, and therefore provides a better opportunity to understand the mechanisms of postprandial glucose change.

## Models and Methods

Various models have been developed and simulated in continuous time to describe and predict change in blood glucose level, and numerous experiments have been designed to define the parameters of these equations. Among them, the two most widely accepted are Bergman's minimal model [4] and Cobelli's two compartment model [5]. The models include multiple variables in order to reflect and adequately describe glucose-insulin dynamics, a multidimensional system. The limitation is that some parameters of these models are not readily measurable, which poses difficulties in the validation of the models and their applicability for prediction of glucose dynamics. This is because accessible experimental data for individual patients diagnosed with diabetes still remain one-dimensional: only one transient variable (the glucose level) as a function of time is available in most situations, representing the response of a complex system to an external influence. In order to overcome this limitation, an entirely different *minimal inference approach* can be employed: development of a *deterministic* model (of a multidimensional system represented by a single time series) by inferring parameters of unrecorded variables [6]. Another challenge, however, is the presence of a strong *stochastic* component: this can be an internal characteristic of the system alone and/or the result of measurement error.

We applied the minimal inference technique in order to define a model based on stochastic differential equations which takes into account the nonlinear character of the blood glucose response to food intake, has minimal order and minimal number of unknown parameters, and is capable of adequately describing the glucose time series and of predicting the glucose dynamics in response to the external stimuli. The advantage of this model, inferred from experimental data, can be quantitatively determined by comparing with the existing deterministic multidimensional models, i.e [4, 5].

The stochastic differential equation for characterisation and prediction of postprandial blood glucose levels has the form

$$\frac{d^2}{dt^2}x_t + f_1(x_t) \frac{d}{dt}x_t + f_2(x_t) = u_t + \eta_t \quad (1)$$

where

$$f_1(x_t) = \sum_{i=1}^n \theta_i x_t^i, \quad f_2(x_t) = \sum_{i=1}^n \theta_{ki} x_t^i, \quad y_t = x_t + \varepsilon_t. \quad (2)$$

Formula (1) is an evolution equation,  $y_t$  is the measured time series from CGM,  $x_t$  is the glucose time series,  $u_t$  is the external glucose intake (impulse action),  $\theta_i$  and  $\theta_{ki}$  are evolution parameters,  $\eta_t$  and  $\varepsilon_t$  are dynamical noises and measurement error respectively.  $f_1(x_t)$  and  $f_2(x_t)$  are polynomial functions of  $x_t$ .

## Results and conclusions

Fifteen glucose profiles for three categories of people (control without diabetes, Type I and and Type II diabetes patients) were available for the study. An example of a glucose time series for one patient is shown in Figure 1: subcutaneous glucose values were taken every 5 minutes over 72 hours using CGMS (Continuous Glucose Monitoring System).

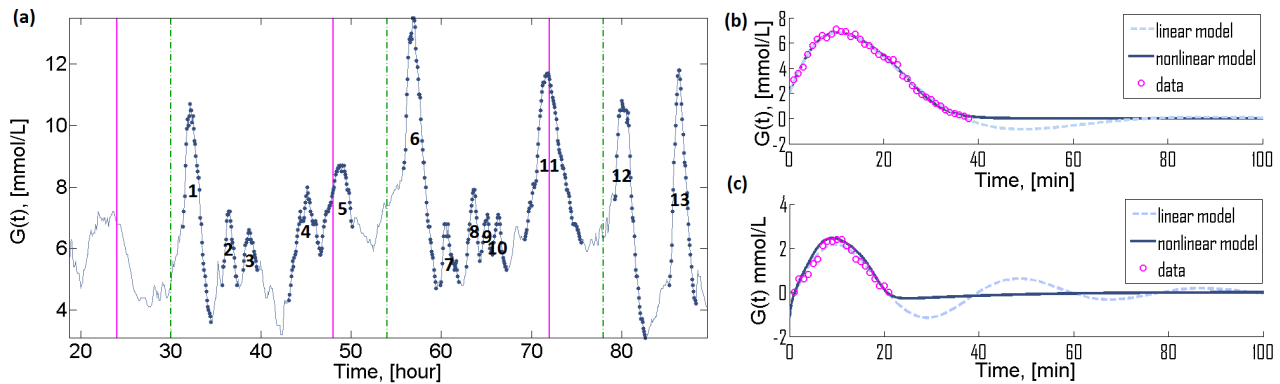


Figure 1: (a) Concentration of subcutaneous glucose level measured continuously over 72 hours  $G(t)$ . Solid line represents the measured glucose values and the dots are the values used for inferring parameters of single prandial events (peaks). The dashed and solid vertical lines corresponds to 6 am and midnight respectively. There were 13 peaks observed over 72 hours as labelled; (b) Fitting for peak 1; (c) Fitting for peak 2.

A variational Bayesian toolbox [7] has been applied to extract the dynamic patterns hidden in noisy data, i.e. to fit available glucose time series by equation (1). Nonlinear functions  $f_1$  and  $f_2$  were optimised by minimising the number of nonlinear parameters  $\theta_i$  and  $\theta_{ki}$  necessary to describe a prandial event (food intake). Various degrees of polynomial nonlinearities in (1) were considered starting with the linear case (linear  $f_1$  and  $f_2$ ) and increasing the complexity of polynomials (2) until a satisfactory fitting had been achieved. It was shown that the transient response of the system to prandial events can be modelled by nonlinear equation (1) of the second order for which  $f_1(x_t) = \theta_{k2}x^2 + \theta_{k1}x + \theta_{k0}$  is a nonlinear function with three unknown parameters and  $f_2(x_t) = \theta_1$  is linear with one unknown parameter. The food intake is modelled by two initial conditions for equation (1).

Comparison of parameters  $\theta_{k2}$ ,  $\theta_{k1}$ ,  $\theta_{k0}$  and  $\theta_1$  for people from different groups showed that linear second order equation ( $\theta_{k2} = 0$ ,  $\theta_{k1} = 0$ ) can be successfully used to model response to food intake of people without diabetes. This conclusion supports the results of [8]. However, in order to describe the dynamics of prandial events for people with Type II diabetes a nonlinear damping term  $f_1(x_t) = \theta_{k2}x^2 + \theta_{k1}x + \theta_{k0}$  had to be included in the model (1) indicating a nonlinear character of the response. It was also noticed that values of parameters vary from peak to peak for a single profile indicating a strong nonlinear dependence of the transient response on the amplitude and time of the external stimuli. For the linear model, parameters  $\theta_k$  and  $\theta_1$  tend to cluster within a different range of values at different times of the day. If all the prandial events are grouped into breakfast, lunch, dinner and snack categories, then the average value for  $\theta_1$  after lunch is smaller than the value after breakfast, and larger than the value after dinner. The values for snacks are spread more widely than those in other categories. The difference in postprandial glucose patterns at different times of the day might be explained by hormone changes throughout the day.

Comparative analysis of the existing models and those suggested by this research is in progress.

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